PTEN, the lipid phosphatase and tensin homologue, is a key tumor suppressor. Mutations resulting in the loss of PTEN or the loss of its function are common and functionally relevant in tumors of different histologic origins, including breast cancer. A recent study by Nagata and colleagues\(^1\) shows that PTEN not only antagonizes tumorigenesis but also sensitizes breast cancers to targeted therapy with trastuzumab (Herceptin), a humanized monoclonal antibody against ErbB2 (also referred to as HER2/neu), a membrane-receptor tyrosine kinase in the epidermal growth factor receptor family.\(^3\)

PTEN normally opposes the activation of the proto-oncogenic phosphatidylinositol 3' kinase

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**Figure 1. Resistance to Trastuzumab Due to PTEN Deficiency.**

In Panel A, the overexpression of ErbB2 leads to its activation through autophosphorylation (P). As a result, Src kinase and phosphatidylinositol 3' kinase (PI3K), with its regulatory subunits p85 and p110, are recruited to the receptor and kept in their active state. The activation of PI3K leads in turn to the activation of the proto-oncogenic signaling pathway consisting of Akt and the mammalian target of rapamycin (mTOR). Nagata and colleagues\(^2\) show that when active, Src can inactivate PTEN through the phosphorylation of its C-terminal end. This triggers the production of elevated levels of phosphatidylinositol 3,4,5-triphosphate (PIP3), further potentiating the activation of PI3K. On binding to the ErbB2 receptor, trastuzumab causes the dissociation of the receptor from Src and its inactivation through unknown mechanisms (Panel B). PTEN thus becomes free to antagonize the activation of the PI3K–AKT–mTOR signaling pathway through the dephosphorylation of PIP3. Trastuzumab could be combined with drugs such as sirolimus (rapamycin) and its analogues, everolimus (RAD001) and CCI-779, which inhibit mTOR, to block this critical signaling pathway at two different points. Nagata et al. show that a partial or total deficiency of PTEN (Panel C) may account for resistance to trastuzumab.\(^2\)
Approximately 50 percent of patients with breast cancer have a mutation in or loss of at least one copy of the \textit{PTEN} gene, which results in the activation of PI3K signaling. The severity of \textit{PTEN} mutations strongly correlates with the tumor stage and grade. For example, complete loss of \textit{PTEN} is more frequent in metastatic cancer than in primary tumors.\(^1\) The loss of one copy of \textit{PTEN} increases the risk that a tumor will develop, and the level of expression of \textit{PTEN} dramatically affects the initiation and progression of tumors.\(^4\) The study by Nagata and colleagues suggests that the gene dose and, therefore, the levels of expression of \textit{PTEN} may also determine the response to therapy.

Up to 30 percent of human breast cancers overexpress ErbB2, as do other types of cancer, and such overexpression correlates with extremely aggressive cancers and a poor prognosis.\(^3\) In addition, intragenic \textit{ErbB2} mutations in the kinase domain of the receptor have recently been identified in lung tumors.\(^5\) Trastuzumab binds specifically to the extracellular domain of ErbB2 (Fig. 1) and can induce down-regulation and inactivation of the receptor through several mechanisms.\(^3\) Inactivation, in turn, results in poorly understood antitumoral responses, including arrest of the cell cycle. Although trastuzumab prolongs survival among patients with cancer when administered with chemotherapy, it does not cure cancer. Furthermore, many patients have primary resistance to trastuzumab for unknown reasons.\(^3\)

Nagata and colleagues provide data that clarify the antitumoral mechanism of trastuzumab and help clarify the mechanism underlying resistance. They show that, on binding to the ErbB2 receptor, trastuzumab stabilizes and activates the \textit{PTEN} tumor suppressor and consequently down-regulates the PI3K–Akt signaling pathway (Fig. 1A).\(^2\) When the expression of \textit{PTEN} is reduced or abrogated, this chain of events is interrupted and the antitumoral effects of trastuzumab are impaired (Fig. 1B). The authors therefore predicted that the presence of low levels of \textit{PTEN} would correlate with unresponsiveness to trastuzumab treatment and subsequently confirmed this correlation in a small group of patients.\(^2\) Prospective studies using larger cohorts of patients and thorough in vivo genetic analyses of mice with various degrees of \textit{Pten} function are warranted.

Because the level of expression of \textit{PTEN} is critical to tumorigenesis and apparently modulates the response to therapy, the systematic analysis of the activation status and level of expression of \textit{PTEN} and PI3K in tumors is now imperative. So, too, are experiments to determine whether gain-of-function mutations in the \textit{ErbB2} and PI3K genes also correlate with unresponsiveness to trastuzumab and other small-molecule inhibitors of \textit{ErbB2}. The new findings call for a renewed focus on \textit{PTEN} as a possible target for therapeutic intervention in tumors that lack one copy of \textit{PTEN}. Drugs that augment \textit{PTEN} levels may sensitize these tumors to trastuzumab and other drugs. One could also envision the therapeutic use of a combination of trastuzumab and PI3K inhibitors (when these become available) or downstream inhibitors of the PI3K–Akt signaling pathway, such as sirolimus (rapamycin) and its analogues.

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